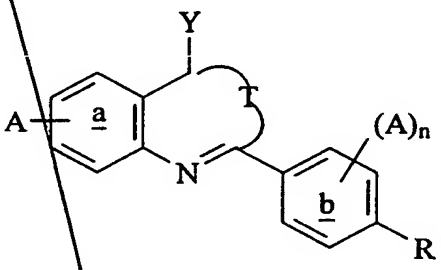
CLAIMS

1. Use of an inhibitor of dihydroorotate dehydrogenase in the manufacture of a medicament for use in the treatment of an infection attributable to a virus of the Flaviridae, Rhabdoviridae or Paramyxoviridae family.

2. Use according to claim 1, wherein the inhibitor is a compound of the formula (I):



(I)

wherein:

each A is independently selected from the group consisting of hydrogen, halogen, perhaloalkoxy, amino C_1-C_8 alkyl, NO_2, CN, SO_2CH_3, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, aryl, aryloxy, C_1-C_6 perhaloalkyl and Y; or

two adjacent groups A on ring b form, together with the phenyl ring to which they are attached, a naphthalene ring system;

R is cyclohexyl, phenoxy or benzoxy, or a phenyl ring which is unsubstituted or substituted by a group A as defined above; or

R and an adjacent group A on ring b form, together with the phenyl ring to which they are attached, a naphthalene or phenanthrene ring system;

Y is selected from the group consisting of COOM, CONHR', SO_3M and hydrogen;

M is selected from the group consisting of H, Li, Na, K and O.5 Ca;

R' is C_1-C_{10} alkyl;

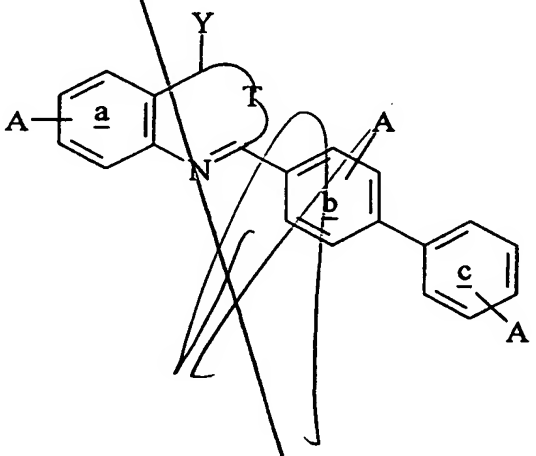
n is 1 or 2; and

T is =N- or =C(Z)- wherein either:

(i) Z is selected from the group consisting of hydrogen, NH_2, OH, C_1-C_8 alkyl, C_3-C_7 cycloalkyl, aryl and C_1-C_6 perhaloalkyl, or

(ii) Z is a bridging moiety selected from the group consisting of -V-W- (wherein V is CH_2 or S and W is CH_2, O, S or NH) and -$(CH_2)_2$ -C(=Z)- wherein Z is O or H_2, the said bridging moiety being attached to the ortho position of ring b of the adjacent biphenyl group, thereby completing a ring.

3. Use according to claim 2, wherein the inhibitor is a compound of formula (Ia):



(Ia)

wherein:

each A is independently selected from the group consisting of hydrogen, halogen, amino C_1-C_8 alkyl, NO_2, CN, SO_2CH_3, C_1-C_8 alkyl, C_3-C_7 cycloalkyl, aryl, C_1-C_6 perhaloalkyl and Y;

Y is selected from the group consisting of COOM, CONHR' SO_3M and hydrogen;

M is selected from the group consisting of H, Li, Na, K and O.5 Ca;

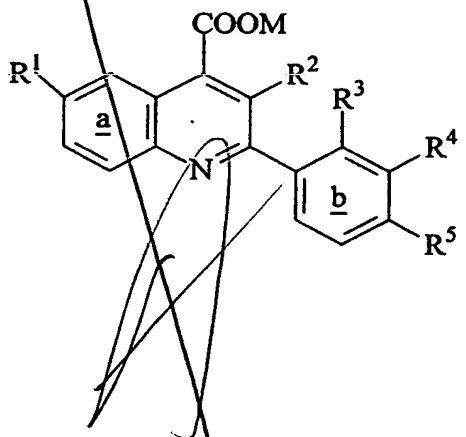
R' is C_1-C_{10} alkyl; and

T is =N- or =C(Z)- wherein either:

(i) Z is selected from the group consisting of hydrogen, NH_2, OH, C_1-C_8 alkyl, C_3-C_7 cycloalkyl, aryl and C_1-C_6 perhaloalkyl, or

(ii) Z is a bridging moiety selected from the group consisting of -V-W- (wherein V is CH_2 or S and W is CH_2, O, S or NH) and $-(CH_2)_2$ -C(=Z)- wherein Z is O or H_2, the said bridging moiety being attached to the ortho position of ring b of the adjacent biphenyl group, thereby completing a ring.

4. Use according to claim 2 or 3 wherein the inhibitor is a compound of the formula (II):



(II)

wherein

R^1 is H, a halogen or OCF_3;

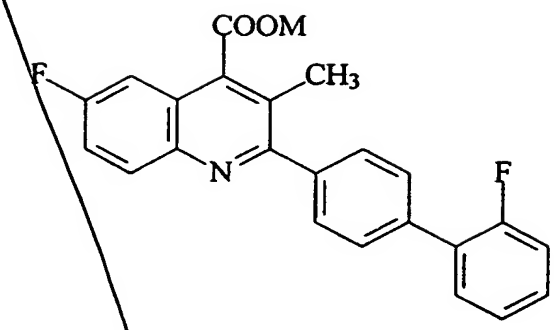
R^2 is H or C_1-C_6 alkyl;

R^3 is H or OR^6 wherein R^6 is H or C_1-C_6 alkyl;

R^4 is H or C_1-C_6 alkyl; or R^4 and R^3 form, together with phenyl ring b to which they are attached, a naphthalene ring; and

R^5 is cyclohexyl, phenyl or benzoxy, or a phenyl ring which is unsubstituted or substituted by halogen; or R^4 and R^5 form, together with phenyl ring b to which they are attached, a phenanthrene ring.

5. Use according to any one of claims 2 to 4 wherein the inhibitor is a compound of formula (IIb):

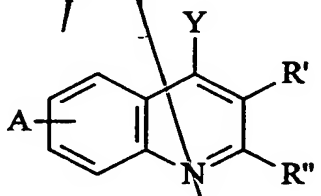


(IIb)

wherein M is H or Na.

6. Use according to claim 1 wherein the inhibitor is a compound of formula (I'):

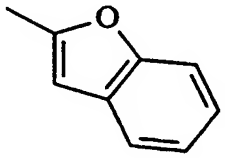
:



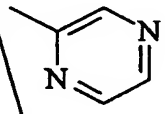
(I')

wherein A and Y are as defined above for formula (I);

R′ is hydrogen and R″ is a thiophene ring or a group of formula (i') or (ii'):

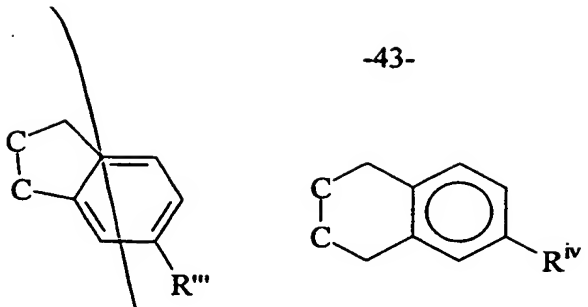


(i')



(ii')

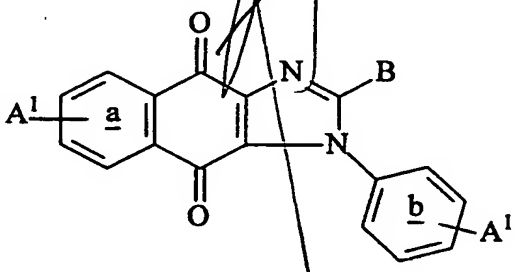
or R′ and R″ form, together with the carbon atoms (denoted "C") to which they are attached, a ring system of formula (iii') or (iv'):



(iii') (iv')

wherein R"' is H or halogen and R^{iv} is H or C_1 - C_6 alkoxy.

7. Use according to claim 1, wherein the inhibitor is a compound of the formula (III):



(III)

wherein:

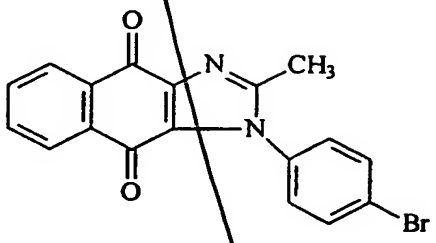
each A^1 is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, halogen, unsubstituted aryl, X-substituted aryl, NO_2, CN, COOR, CONHR and NHR;

X is selected from the group consisting of halogen, NO_2, C_1-C_8 alkyl, aryl, fused aryl and COOR;

R is selected from the group consisting of hydrogen and C_1-C_8 alkyl; and

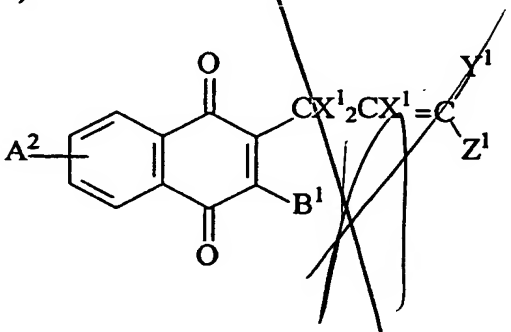
B is selected from the group consisting of C_1-C_8 alkyl, H, CF_3 and aryl which is unsubsituted or substituted by halogen, C_1-C_8 alkoxy, C_1-C_8 alkyl, NO_2, aryl or fused aryl.

8. Use according to claim 7, wherein the inhibitor is a compound having the formula (IV):



(IV)

9. Use according to claim 1, wherein the inhibitor is a compound having the formula (V):



(V)

wherein:

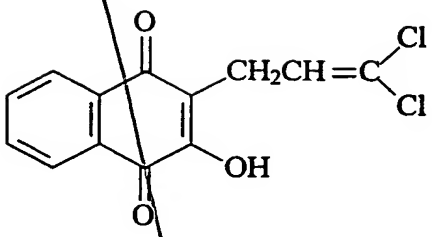
A^2 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_7 cycloalkyl, halogen, unsubstituted aryl, halogen-substituted aryl, fused aryl, NO_2, CN, NHR^1 and $N(R^1)_2$;

R^1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl and OH;

X^1 is hydrogen or halogen; and

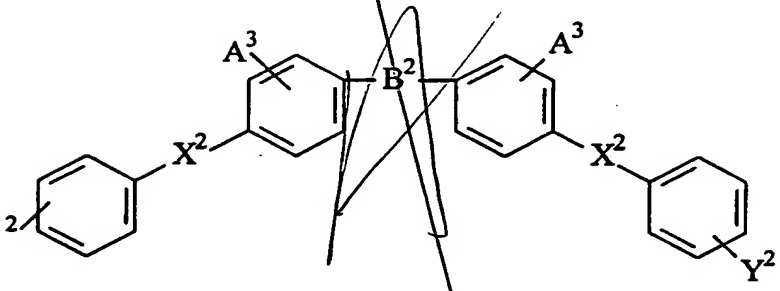
B^1, Y^1 and Z^1 are each independently selected from hydrogen, OH, C_1-C_8 alkyl, halogen, CN, NO_2 and CF_3.

10. Use according to claim 1, wherein the inhibitor is a compound having the formula (VI):



(VI)

11. Use according to claim 1, wherein the inhibitor is a compound having the formula (VII):



(VII)

wherein:

each A^3 is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_{10} alkoxy, halogen and $N(R^2)_2$;

B^2 is a direct bond, -CH=CH- or -C≡C-;

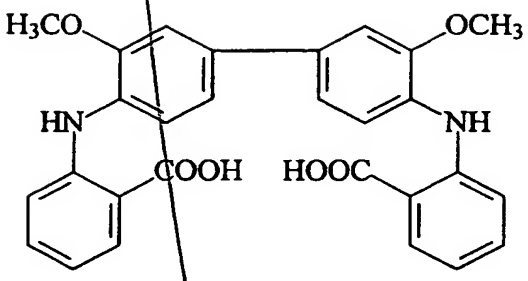
X^2 is selected from the group consisting of O, S and NR^2;

R^2 is selected from the group consisting of hydrogen, C_1-C_4 alkyl and aryl;

Y^2 is selected from the group consisting of $COOM^1$ and SO_3M^1; and

M^1 is selected from the group consisting of H, Li, Ha, K and 0.5 Ca.

12. Use according to claim 11, wherein the inhibitor is a compound having the formula (VIII):



(VIII)

13. Use according to any one of the preceding claims wherein the virus is a flavivirus selected from the group consisting of hepatitis viruses, yellow fever virus, West Nile virus, kunjin virus, dengue virus, St. Louis encephalitis virus, Japanese encephalitis virus, Murray valley encephalitis virus and tick-borne encephalitis virus.

14. A method according to any one of claims 1 to 13, wherein the virus is a rhabdovirus selected from vesicular stomatitis virus and rabies virus, or is the paramyxovirus RSV.

15. Use according to any one of the preceding claims wherein the medicament is for administration with an interferon.

16. Use according to any one of the preceding claims wherein the medicament further comprises an interferon.

17. Use according to claim 15 or 16, wherein the interferon is a human interferon.

18. Use according to claim 17, wherein the interferon is selected from the group consisting of interferon α2, interferon α8 and interferon β.

19. Use according to claim 18, wherein the interferon is human interferon α8 having a specific activity of from $0.3x10^9$ to $3x10^9$ IU per mg protein.

20. Use according to claim 18, wherein the interferon is human interferon β having a specific activity of from $2x10^8$ to $8x10^8$ per mg protein.

21. Use according to any one of claims 15 to 20 wherein the inhibitor and the interferon are used in respective amounts which produce a synergistic effect.

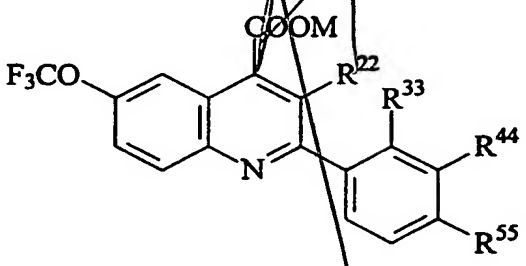
22. Use according to any one of the preceding claims wherein the medicament is for use with an inhibitor of a second enzyme selected from inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, cytidine triphosphate synthetase and S-adenosylhomocysteine hydrolase.

23. Use according to claim 22 wherein the medicament further comprises the inhibitor of the said second enzyme.

24. Use according to claim 22 or 23 wherein the inhibitor is mycophenolic acid, cyclopentenyl cytosine (CPE-C) or 3-deazaneplanocin A.

25. Use according to any one of claims 22 to 24 wherein the inhibitor of the second enzyme and the inhibitor of dihydrooratate dehydrogenase are used in respective amounts which produce a synergistic effect.

26. A compound of formula (IIa):



(IIa)

wherein

M is selected from the group consisting of H, Li, Na, K and 0.5 Ca;

R^{22} is H or C_1-C_6 alkyl;

R^{33} is H or OR^6 wherein R^6 is H or C_1-C_6 alkyl;

R^{44} is H or C_1-C_6 alkyl; and

R^{55} is phenyl, cyclohexyl, phenoxy or benzoxy;

or a metabolite or prodrug precursor thereof..

27. A compound according to claim 26 which is selected from:

2-(4-biphenylyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K5);

2-(4-biphenylyl)-3-methyl-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K55);

2-(4-cyclohexylphenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound

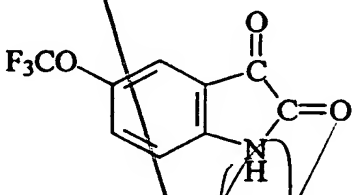
I2K46);

2-(4-benzyloxy-2-methoxy-3-methyl-phenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K51); and

2-(4-phenoxyphenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K52).

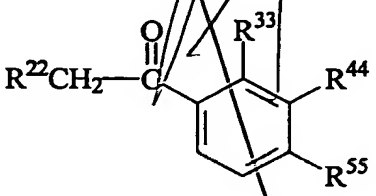
28. A process for producing a compound of formula (IIa) as claimed in claim 26, which process comprises

a) condensing a trifluoromethoxy-substituted isatin compound of the following formula (IX):



(IX)

with a ketone of formula (X):



(X)

wherein R^{22}, R^{33}, R^{44} and R^{55} are as defined in claim 26, in the presence of a base; and

(b) if desired, converting a resulting compound of formula (IIa) in which M is H into a pharmaceutically acceptable salt thereof wherein M is Li, Na, K or 0.5 Ca.

29. A method of treating a host infected with a virus of the Flaviviridae, Rhaboviridae or Paramyxoviridae family, which method comprises administering to the host an inhibitor of dihydroorotate dehydrogenase.

30. An anti-flavivirus, anti-rhabdovirus or anti-paramyxovirus agent comprising an inhibitor of dihydroorotate dehydrogenase.

31. Products containing an inhibitor of dihydroorotate dehydrogenase and

an interferon as a combined preparation for simultaneous, separate or sequential use in treating an infection attributable to a virus of the Flaviviridae, Rhabdoviridae or Paramyxoviridae family.

32. Products containing an inhibitor of dihydroorotate dehydrogenase . and an inhibitor of a second enzyme selected from inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, cytidine triphosphate synthetase and S-adenosylhomocysteine hydrolase as a combined preparation for simultaneous, separate or sequential use in treating an infection attributable to a virus of the Flaviviridae, Rhabdoviridae or Paramyxoviridae family.

33. Products according to claim 32 which additionally contain an interferon.

34. A method for identifying an anti-flavivirus, anti-rhabdovirus or anti-paramyxovirus agent, which method comprises:

(a) providing a test compound;

(b) determining whether the test compound has activity as an inhibitor of dihydroorotate dehydrogenase; and

(c) selecting the test compound as an anti-flavivirus, anti-rhabdovirus or anti-paramyxovirus agent if it is shown to have activity in step (b).

Add A2